

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re application of:) Examiner: Landsman, Robert S.
Avi ASHKENAZI, et al.)
Application Serial No. 09/993,748) Art Unit: 1647
Filed: November 14, 2001) Confirmation No: 4944
For: **PRO1346 POLYPEPTIDES**) Attorney's Docket No. 39780-2730 P1C23
Customer No. 35489)
)

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ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES
APPELLANTS' REPLY BRIEF

MAIL STOP APPEAL BRIEF - PATENTS

Commissioner for Patents -
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

On November 5, 2004, the Examiner made a final rejection to pending Claims 119-127 and 129-131. A Notice of Appeal was filed on January 10, 2005, and Appellants' Appeal Brief was filed August 10, 2005.

An Examiner's Answer was mailed on September 6, 2005. The following constitutes Appellants' Reply Brief in response to the Examiner's Answer. This Reply Brief is accompanied by a Request for Oral Hearing.

ARGUMENTS

Claim Rejections Under 35 U.S.C. §102

Appellants note the Examiner's withdrawal of the rejection of Claims 119-127 and 129-131 under 35 U.S.C. §102(b) over Baker *et al.*

Claim Rejections Under 35 U.S.C. §101

Claims 119-127 and 129-131 stand rejected under 35 U.S.C. §101 as allegedly lacking a specific, substantial and credible asserted utility or a well established utility. Appellants rely on data from the mixed leukocyte reaction (MLR) assay for patentable utility of the claimed PRO1346 polypeptides. The specification discloses that PRO1346 showed positive activity in the MLR assay (as shown in Example 151). The MLR is a well-established assay for evaluating test compounds for their ability to stimulate T-lymphocyte proliferation *in vitro*. The specification explains that compounds which stimulate proliferation of lymphocytes in this assay, such as PRO1346, "are useful therapeutically where enhancement of an immune response is beneficial." Stimulators of T-cell proliferation find utility in fighting viral infections, including retroviral infections, such as HIV infection or Epstein-Barr infection, as well as in the treatment of cancers such as melanoma. The legal standard recognizes that *in vitro* or animal model data is acceptable to establish utility as long as the data is "reasonably correlated" to the pharmacological utility described. Accordingly, a valid case for utility has been made and would be considered credible by a person of ordinary skill in the art.

The Patent Office argues that the MLR assay is not predictive of *in vivo* therapeutic effects, and thus the MLR data is not "reasonably correlated" to the described methods of treating disease. In particular, the Patent Office asserts that if "the mechanism of action of these diseases was that simple and the MLR assay was so well known and reliable at the time of the present invention as to be able to predict *in vivo* results from a positive *in vitro* test then all cancers, HIV/AIDS, viral infections, or any other disease which would benefit from increased T cell production or stimulation, as is the case for MLR, would have been treated/cured." (Page 7 of

the Examiner's Answer). The Examiner's Answer concludes that "the claims of usefulness are not believable on their face." (Page 8 of the Examiner's Answer).

Appellants respectfully submit that the Patent Office misinterprets Appellants' assertion of utility, and, based on this faulty interpretation, is applying an improper legal standard for utility. Nowhere in the specification, or in the arguments submitted during prosecution or the present appeal proceedings have Appellants asserted that, based on the MLR assay data, the PRO1346 polypeptides would be useful to treat, let alone cure, all cancers and viral infections. Rather, Example 151 states: "Compounds which stimulate proliferation of lymphocytes are useful therapeutically where enhancement of an immune response is beneficial." In referring to this statement, Appellants have later explained that enhancement of an immune response is, for example, beneficial in the treatment of patients diagnosed with cancer or viral infections. One of ordinary skill in the art would clearly understand that a statement that a cancer patient or a patient suffering from viral infection benefits from the enhancement of his or her immune response does not mean that the cancer or the viral infection is "cured." What it means is that patients with an enhanced immune response are more likely to respond well or tolerate other treatments, may survive longer, show lesser side effects, or, in the case of certain viral infections which have a known cure, may have a shorter time of recovery. The Examiner has offered no reason why this assertion of utility would not have been credible to one of ordinary skill in the art at the time the invention was made.

It follows that Appellants need not demonstrate, as the Examiner's Answer appears to require, how to use the claimed invention to treat (or cure) cancers and viral infections, let alone to treat (or cure) all cancers and viral infections, since these are not the utilities asserted in the present application.

Nor is it necessary to assert such utilities in order to demonstrate a practical utility. Appellants respectfully note that tests evidencing pharmacological activity of a compound are sufficient to establish practical utility, even though they may not establish a specific therapeutic use. In *Nelson v. Bowler*,¹ the court held that "since it is crucial to provide researchers with an

¹ *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."² In *Cross v. Iizuka*,³ the claimed compounds were found to possess an *in vitro* inhibitory activity for thromboxane synthetase in human or bovine platelet microsomes. Iizuka's priority application also asserted that the claimed compounds were useful in the treatment of diseases caused by thromboxane A2, such as inflammation, hypertension, thrombus, cerebral apoplexy, and asthma, but did not demonstrate actual use in the treatment of any of these diseases, let alone as cures. The C.A.F.C. nonetheless found that the *in vitro* inhibitory activity was sufficient to demonstrate a practical utility, noting that "a rigorous correlation [between the disclosed *in vitro* utility and *in vivo* activity] is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence."⁴ The C.A.F.C. found utility for the claimed compounds based upon the correlation between the *in vitro* activity of the compounds as inhibitors of thromboxane synthetase, an enzyme involved in the synthesis of thromboxane A, and the role of thromboxane A in platelet aggregation, accepting that compounds which reduced levels of thromboxane A would have beneficial effects in the treatment of diseases associated with platelet aggregation even if they did not of themselves cure any or all such diseases.

The instant application discloses an *in vitro* pharmacological utility for the claimed PRO1346 polypeptides, stating in Example 151 that "certain polypeptides of the invention are active as a stimulator of the proliferation of stimulated T-lymphocytes," based upon the results of the MLR assay. In 1998 it was well known in the art, as it is today, that T-cells are highly important in the body's natural defense mechanisms for fighting infections. For example, viral infections, such as HIV infection, are well known to result in reduced T cell count. Indeed, the count of T-cell lymphocytes is a generally accepted measure of the extent and seriousness of HIV infection and resultant AIDS. Accordingly, one of skill in the art would have understood that

² *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

³ *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

⁴ *Id.* at 747, 206 U.S.P.Q. at 739.

stimulators of T-cell proliferation find utility in fighting viral infections, including retroviral infections, such as HIV infection or Epstein-Barr infection.

It was also well known at the time of filing that T cells can recognize tumor antigens and kill tumors. See, for example. Thurner *et al.*, J. Exp. Med. 190:1669-1678 (1999) (submitted as Exhibit E with the Response filed September 9, 2004), which describes experimental procedures designed to treat melanoma by boosting the immune response. Steinman *et al.*, a review article published in December 2000, (submitted as Exhibit B with the Response filed September 9, 2004) teaches that it was also known to be the case that "protein antigens often are known for a tumor-like melanoma, or for a virus like HIV-1 whose genetic sequence has been available," but that these antigens needed to become immunogenic, that is, capable of inducing a T cell response (page 585, col. 1; emphasis added). Thus one of ordinary skill in the art would have reasonably expected that the addition of a molecule that stimulates the proliferation of T-cells that have been activated by dendritic cells would improve the effectiveness of this treatment strategy. The postfiling paper by Peterson *et al.* (Journal of Clinical Oncology 21 (12). 2342-48 (2003) (submitted as Exhibit D with the Response filed September 9, 2004) confirms that this was the case for the immunostimulant molecule IL-12, which provided superior results in this treatment for melanoma. Accordingly, one of skill in the art at the time of filing would have reasonably correlated the demonstrated activity of PRO1346 as a stimulator of the proliferation of stimulated T-lymphocytes to utility in the treatment of viral infections such as HIV infection or Epstein-Barr infection, and cancers such as melanoma.

The Examiner's Answer asserts that using the MLR assay to conclude that one can treat cancer is similar to saying that a compound which reduces cholesterol can prevent heart attacks (Page 8 of the Examiner's Answer). As discussed above, a finding of pharmacological activity does not require demonstrated ability to "cure" any diseases, but only a reasonable correlation with an *in vivo* treatment of at least one disease. Appellants note that while a cholesterol lowering agent is not a "cure" for heart disease, agents that lower cholesterol are in fact widely prescribed to heart disease patients. While lowering cholesterol does not cure or even directly treat heart disease, it improves the overall health of the circulatory system, and results in improved outcomes for heart disease patients, including reduced death rates and decreased need

for surgery. An agent with a demonstrated pharmacological activity in lowering cholesterol would have a clear practical use, and would surely be considered to have patentable utility.

Similarly, a molecule with demonstrated pharmacological activity as a stimulator of the proliferation of stimulated T-lymphocytes, such as PRO1346, would be useful therapeutically where enhancement of an immune response is beneficial, for example in the treatment of patients diagnosed with cancer or viral infections. Just as cholesterol lowering agents provide beneficial effects to heart disease patients without curing the existing heart disease, an agent that enhances the immune response need not be itself a cure for disease in order to have beneficial effects. One of ordinary skill in the art would clearly understand that patients with an enhanced immune response are more likely to respond well or tolerate other treatments, to survive longer, show lesser side effects, or, in the case of certain viral infections which have a known cure, have a shorter time of recovery. In the particular example of melanoma, as discussed above, immunostimulants such as IL-12 are not cures for cancer, but still provide benefits for patients by improving the effectiveness of current treatment protocols.

Finally, Appellants wish to clarify a few remaining points that appear to be misunderstood. The Examiner's Answer asserts that there "appears to be a contradiction in the relationship between DCs and T-cells" between the Fong Declaration and the Appeal Brief, in that "the order of T-cell and DC activation is reversed in these two statements." (Page 9 of the Examiner's Answer). There is no such contradiction. The quoted statement from the Appeal Brief refers to the ability of the test molecules (such as PRO1346) to enhance the effect of the DCs in stimulating T-cells, not to any feedback effect of the T cells on the DCs. As previously explained in Appellants' Brief, the function of DCs is to convert antigens into immunogens for T cells, thus inducing a T cell response, including proliferation of responsive T cells. Activity in the MLR assay demonstrates ability of a test molecule to enhance the proliferation of the T cells which have been stimulated, so they proliferate even more than they normally would. Thus the effect of such positive test molecules is to enhance the function of the DCs, by amplifying the effect of the DCs on T-cell proliferation.

The Examiner's Answer states that while the examples given in the Brief include the use of the MLR assay to find agents useful in the treatment of diseases including viral infections such

as HIV and cancers such as melanoma, "it appears that the only disease actually studied is melanoma." (Page 9 of the Examiner's Answer). It is, however, established that "[g]enerally speaking, utility in treating a single disease is adequate basis for the patentability of a pharmaceutical compound under 35 U.S.C. 101."⁵ Thus even if the claimed compound were only useful in the treatment of melanoma (which Appellants do not concede), this would still be sufficient to demonstrate patentable utility. The Examiner's Answer further asserts that "[t]his specific teaching is not disclosed in the specification." (Page 9 of the Examiner's Answer). As discussed above, Example 151 disclosed that PRO1346 had *in vitro* pharmacological activity as a stimulator of the proliferation of stimulated T-lymphocytes. As evidenced by the Thurner *et al.* and Steinman *et al.* references, it was known in the art at the time of filing that stimulated T-cells could recognize tumor antigens and kill tumors, and that the main barrier to using this as an effective anti-cancer therapy was increasing the immunogenicity of tumor antigens. Further, it was well known in the art that "**the majority of tumor antigens identified so far are expressed by melanomas**" (Thurner *et al.*, page 1669, col. 2; emphasis added). Thus one of ordinary skill in the art would clearly have been guided to the conclusion that melanoma was a logical disease candidate for which enhancement of the T-cell response would provide beneficial effects in treatment.

The Examiner's Answer also disputes the relevance of the Gubler *et al.* article, pointing out certain points of difference in the assay of Gubler *et al.* as compared to the disclosed MLR assay. As explained in the Appeal Brief, while Gubler *et al.* did not use the same MLR assay as disclosed in the instant specification, they used a similar *in vitro* assay of T-cell proliferation, confirming Appellants' assertion that such *in vitro* systems are predictive of *in vivo* efficacy. Appellants note that IL-12 was shown to induce the proliferation of PHA-activated peripheral blood lymphocytes on its own, not synergistically with IL-2 (page 4145, col. 2). The Examiner's Answer asserts that Gubler *et al.* does not demonstrate that *in vitro* results can be extrapolated to *in vivo* efficacy. (Page 10 of the Examiner's Answer). Appellants respectfully submit that the stated purpose of the experiments in Gubler *et al.* was to find cytokines that would have

⁵ *Ex parte Krepelka*, 231 U.S.P.Q. 746, 747 (PO BdPatApp & Inter. 1980).

immunoenhancing effects *in vivo*. The authors' choice of an *in vitro* assay similar to the MLR assay disclosed in the instant application demonstrates that those skilled in the art understood such assays to be reasonably correlated with *in vivo* immunoenhancing effects. The results of the postfiling Peterson paper merely confirmed this correlation.

In summary, Appellants reiterate that the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. In order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. With respect to asserted therapeutic utilities based upon *in vitro* data, an applicant "does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty."⁶ The law requires only that one skilled in the art should accept that such a correlation is **more likely than not to exist**.

Appellants respectfully submit that the Examiner has not shown that it is more likely than not that one of ordinary skill in the art would doubt the truth of Appellants' statement of utility. Appellants have provided a Declaration from an expert in the art which supports the statements in the specification as filed that molecules such as PRO1346, which test positive in the MLR assay, have therapeutic utility as immunostimulants. The art of record, such as Gubler *et al.*, confirms that *in vitro* assays such as the MLR assay can be successfully used to identify compounds having immunomodulatory activity *in vivo*. One of skill in the art would understand that, as disclosed in the specification, compounds which stimulate proliferation of lymphocytes are useful therapeutically where enhancement of an immune response is beneficial, for example, in the treatment of patients diagnosed with cancer or viral infections. The Patent Office has not cited any references or other evidence to demonstrate that one of ordinary skill in the art would find it more likely than not that molecules which test positive in the disclosed MLR assay would not have real-world therapeutic utility. Thus the Patent Office has failed to meet its initial burden of proof that Appellants' claims of utility are not substantial or credible.

⁶ M.P.E.P. 2107.03.

For the reasons given above, Appellants respectfully submit that the results of the MLR assay as shown in Example 151 of the present specification provide a specific, substantial and credible utility under 35 U.S.C. §101 for the claimed invention.

Claim Rejections Under 35 U.S.C. §112, First Paragraph - Enablement

A. Claims 119-127 and 129-131 also stand rejected under 35 U.S.C. §112, first paragraph, for essentially the same reasons. Appellants respectfully submit that, as discussed above, the MLR assay demonstrates utility for the PRO1346 polypeptide for the treatment of conditions where the stimulation of activated T-cell proliferation would be beneficial, including viral infections such as HIV and Epstein-Barr, and cancers such as melanoma. Thus one of ordinary skill in the art would have understood how to use the claimed polypeptides, for example in the treatment of viral infections such as HIV and Epstein-Barr, and cancers such as melanoma.

B. The Examiner's Answer further maintains that even if the claims possessed utility under 35 U.S.C. §101, claims 119-127 and 129-131 would still be rejected under 35 U.S.C. §112, first paragraph, "because the specification, while then being enabling for SEQ ID NO:313 and 314, does not reasonably provide enablement for polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity to SEQ ID NO:314, to the protein encoded by ATCC No. 203128 ... or for fusion proteins." (Page 5 of the Examiner's Answer).

Appellants have previously noted that the claimed variants all share the functional limitation that "said polypeptide is an immunostimulant." Further, Example 151 of the present application provides detailed protocols for the MLR assay, including the extensive step-by-step guidance from Current Protocols in Immunology, which is explicitly incorporated into the specification by reference. The Examiner's Answer asserts that "the breadth of the claims remains excessive since the functional limitation is general." (Page 12 of the Examiner's Answer). In particular, the Examiner asserts that since "the claims are not limited to polypeptides which are shown to be immunostimulatory in the MLR assay, it includes in breadth the stimulation of the immune system by polypeptides which can stimulate the immune system in other ways, such as activation of B cells. Appellants have not provided any guidance or working examples of polypeptides which can stimulate immune cells other than via the MLR." (Page 12 of the Examiner's Answer).

Appellants recognize that there may be polypeptides that stimulate the immune system through mechanisms unrelated to those of PRO1346, and thus do not resemble PRO1346 in structure. These structurally unrelated polypeptides, however, would not be encompassed by claims requiring at least 80% amino acid sequence identity to SEQ ID NO:314. Appellants claim only those proteins which meet both limitations of the claims, structural and functional. Given the structural limitation, the additional functional limitation clearly acts to further define the claimed genus.

Accordingly, Appellants submit that the identification of variant PRO1346 polypeptides having at least 80% identity to SEQ ID NO:314 wherein the polypeptide is an immunostimulant, can be performed by techniques that were well known in the art at the priority date of this application, and that the performance of such work does not require undue experimentation.

CONCLUSION

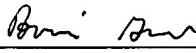
For the reasons given above, Appellants submit that the MLR assay disclosed in Example 151 of the specification provides at least one patentable utility for the PRO1346 polypeptides of Claims 119-127 and 129-131, and that one of ordinary skill in the art would understand how to use the claimed polypeptides, for example in therapeutic applications where enhancement of an immune response is beneficial, such as the treatment of viral infections or cancer. Therefore, Claims 119-127 and 129-131 meet the requirements of 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

Accordingly, reversal of all the rejections of Claims 119-127 and 129-131 is respectfully requested.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (referencing Attorney's Docket No. 39780-2730P1C23).

Respectfully submitted,

Date: November 4, 2005

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